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ANNUAL PROGRESS REPORT

Report Prepared By: José M.R. Delgado, M.D. Date: 15 January 1954
For period: Nov. 1 - Dec. 31, 1953

AR: 113-320

CONTRACT: SAR/Nonr-609(08)

ANNUAL RATE: \$7,950.00

CONTRACTOR: Yale University

PRINCIPAL INVESTIGATOR: Jose M.R. Delgado, M.D.
Assistant: Arnold Schulman

TITLE OF PROJECT: NEUROLOGICAL MECHANISMS IN EPILEPSY

Objectives: To study in unanesthetized animals the role of various cerebral structures in the onset, spread and clinical manifestations of the epileptic attack. The relation between cerebellum and cortical motor areas will also be considered.

ABSTRACT OF RESULTS

The present project was activated on November 1, 1953, therefore we are reporting only two months of work. In this period we have prepared five cats and two monkeys with multilead electrodes implanted within the brain structures. All the animals are alive and in good condition.

Method

The electrodes used are of two types: a needle electrode for implantation within the brain and a plate electrode for placement against the brain cortex. Each electrode consists of six wires of enamelled stainless steel, each wire being .005 inches in diameter and insulated except for 1 mm. distance at the tip. The exposed tips are in turn separated by an interval of 2 mm. for the motor area and 1 mm. for the cerebellum. The six wires are enclosed in polyethylene tubing and the total diameter of the needle electrodes lying inside the brain is .5 mm. The six wires are attached to a sub-miniature radio tube socket which rests on the outside of the head of the animal. By means of this socket, connection is made with the stimulator or with the electroencephalograph. These needle electrodes are implanted within the brain with aseptic precautions, with the animal under anesthesia and using a Horsley-

Clarke stereotaxic instrument. Needle electrodes are implanted in the motor area at the coordinate A-25, lateral 5. In the cerebellum the needle electrodes are implanted with a 15 degree angle at a level varying from 3 to 6 mm. above the 0 plane, 7 to 10 mm. from the middle line. In three cats plate electrodes were also inserted under the dura on the ansiform lobule of the cerebellum. The use of two Grass type S-4 stimulators with stimulus isolation units, type 4-A, allows the parameters of stimulation of the two areas to be varied independently. A relay is used when simultaneous firing of both stimulators is desired. A rotor timing device is employed to ensure a one minute delay between stimulations, as well as a two second stimulation period. Electroencephalographic recordings are made on a console model IIID, 8 channel Grass recorder, and they are monitored in a 2 beam Dumont oscilloscope, type 322.

Motor Defects as a Result of Electrode Implantation

No observable detrimental effects were caused by implantation of needle electrodes in either the cerebellum or motor areas in the cats or monkeys.

Plate electrodes were employed in the cerebellum and not in the motor area. In several of the animals so studied, it was found that a hind limb deficit occurred with no apparent changes in the fore limbs; this deficit in the hind limbs was observed only when the animal attempted voluntary movement. When attempting to walk, an extension of both hind limbs occurred which seemed to check any further forward movement. For about a week following electrode implantation, definite equilibratory defects were noted in several of the animals. They tended to fall to the side in which the plate electrode had been implanted in the cerebellum.

The hyperextensibility noted above appears to be in accordance with Fulton's (1) contention, based on his extensive ablation studies on the cerebellum, that the greater tonicity of the anti-gravity musculature occurs as a result of hyperexcitability of the stretch receptors. A similar effect of

cerebellar ablation was noted to occur in the placing reaction, which also became hyperreactive.

Electroencephalographic Recordings

In the literature there is little information concerning the simultaneous electrocorticographic recording of several different points of the cerebrum and cerebellum in unanesthetized, unrestrained animals. In monkeys we have seen that it is difficult to avoid movements artefact and therefore restraint was necessary in order to get good recordings. The cats in general lay down peacefully without restraint and were not disturbed by the presence of the electrodes nor the connecting leads and recordings were easy to take.

In this manner we are accumulating data on different days, which will be used as the baseline for our future studies to learn possible changes induced by electrical stimulation of different points, and eventually by administration of drugs. A very pleasant feature is that recordings were alike on different days.

Results of Electrical Stimulation

The electrical stimulation of the superficial and hidden motor cortex in the cat evoked a wide variety of movements. The hind limbs were mainly represented in the hidden portions of the sulcus cruciatus, and the face and the fore limbs were represented in the inferior part of the sulcus presylvius, confirming in this way some of our previous studies. The effect of stimulating the cerebellum, in which our collaborator Arnold Schulman has been mainly engaged, has been very interesting. The motor effects resulting from stimulation of the neocerebellum were indistinguishable in most respects from those resulting from motor cortical stimulation. At threshold values, the movements were well coordinated and occurred only during stimulation. At higher voltages, after discharges occur, and at still higher stimulation values cerebellar seizures of the type described by Clark (2) were brought about.

The movements elicitable from the cerebellum consisted of opening the mouth,

licking, squinting of the eyes, movements of the facial musculature, scratching, and flexing of both the fore and hind limbs. These motor effects appeared upon stimulation in a manner similar to movements resulting from motor cortical stimulation; the characteristics of the responses were in fact so similar that by only observing the evoked responses it was not possible to guess whether the cerebellum or the cerebral areas were stimulated. It can therefore be stated that the movements elicited from the neocerebellum did not lack the explosive quality of those resulting from motor cortical excitation.

Although the same points in the cerebellum gave the same motor responses at essentially the same threshold of stimulation on successive days of stimulation, no clear out spatial representation of movement was apparent in the neocerebellum. While there was a tendency of the head and fore limb movements to occur from the more anterior portion of the ansiform lobule and for the posterior portion to elicit posterior limb movement, no definite statements can be made at this point as to how definite this representation actually is.

Simultaneous Stimulation of the Cerebellum and Motor Areas

Simultaneous stimulation of both the cerebrum and neocerebellum was carried out utilizing two stimulators of identical design, thereby allowing the independent variations of the parameters in each area. Simultaneous fixing of the two stimulators was accomplished by means of a relay device. The areas were stimulated at constant one minute intervals for a period of two seconds by means of a rotor timing device.

Control periods, equal in length to the experimental period, were first run for a given set of points in the cerebellum and motor areas. The constancy of the threshold of stimulation, as well as the amplitude of the response was noted. It was found that the animal could recover completely from this control study relatively rapidly (in an hour) but to ensure an adequate recovery five hours were allowed between the control and experimental periods.

Stimulation of points in the cerebellum and motor areas at values determined during the control period and then rechecked immediately before the experimental period resulted in rather consistent results. It was found that stimulation of the cerebellum at 90%, 100%, and 110% of its previously determined threshold value caused no changes in the threshold for response emanating from the motor cortex. The cerebellar and cerebral motor responses occurred in an independent but well coordinated manner. For example, if the cerebellar area in question gave a turning of the head to the right, and the motor area a lifting of the right forepaw, then simultaneous stimulation of the two areas resulted in a well coordinated movement in which the animal simultaneously lifted its right forepaw and turned his head to the right.

PLANS FOR FUTURE:

In only two months of work naturally the project is in its very first stage, and our plans for the future are as stated in our original proposal for contract.

The only departure is in the study of anoxic anoxia which was dependent on the availability of the strato-chamber. This chamber is no longer in use and the University is planning to remove it. Therefore we shall devote all our time to the other two problems of our project, namely, neurological mechanisms in epilepsy, and relations between cerebellum and cortical motor areas.

References:

- (1) Fulton, J.F., Textbook of Physiology. 16th ed., 1949, W.B. Saunders Co., Philadelphia.
- (2) Clark, S.L. Responses following the electrical stimulation of the cerebellar cortex in the normal cat. J. Neurophysiol., 1959, 2:19-37.